

Metronidazole in a single dose for the treatment of trichomoniasis

Failure of a 1-g single dose

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SUMMARY To determine the minimum effective dose of metronidazole in the treatment of vaginal trichomoniasis, a randomised clinical trial comparing single 1-g and 2-g doses was carried out on 163 patients attending sexually transmitted diseases and family planning clinics. Seventy-two of 86 (84%) patients receiving a single 2-g dose of metronidazole were cured compared with only 42 of 77 (55%) receiving a 1-g dose. The body weight of the patient was a significant variable affecting treatment outcome only in the latter group; 69% of patients weighing more than 57 kg or less were cured compared with only 43% of those weighing more. Patients who failed after either dose regimen were retreated with a single 2-g dose. Eighteen of 21 (86%) and seven of 10 (70%) failures with the initial 1-g and 2-g doses respectively were cured. A single 1-g dose of metronidazole is not recommended as routine treatment for vaginal trichomoniasis.

Introduction

A single 2-g dose of metronidazole is recognised as an effective treatment for trichomonal vaginitis and gives comparable results to the standard seven-day course of 250 mg three times daily.¹⁻¹¹ The minimum single dose has not, however, been well established, although the efficacy of single 1-g and 1.5-g doses was reported by one investigator to be equivalent to a 2-g dose.^{6, 7} The purpose of this study was to confirm the preceding results with a 1-g dose in the hope of determining the lowest effective dose of metronidazole for routine use in trichomoniasis in order to minimise costs and any potential toxicity of the drug.

Patients and methods

From March 1978 to April 1980 a total of 186 female patients, 84 attending the sexually transmitted diseases clinic and 102 the family planning clinic at Middlesex-London District Health Unit, London, Ontario, Canada, were enrolled in a randomised single-blind prospective study, in which single 1-g and 2-g doses of metronidazole were compared. Patients were

informed of the nature of the trial and follow-up procedures before entry into the study.

The diagnosis of trichomoniasis was initially suspected clinically in patients who complained of increased or malodorous vaginal discharge and perineal pruritus or soreness. This was confirmed by speculum examination, demonstration of viable trichomonads in a wet-mount preparation, and subsequent culture of the organism from vaginal secretions in modified Diamond's medium. After entry into the study, the patient's body weight and symptoms were recorded and she was randomly assigned to receive either a single 1-g or 2-g dose of metronidazole by a series of random numbers prepared by the pharmacy. The drug was dispensed as 250-mg tablets of Flagyl® (Rhone-Poulenc Pharma Inc, Montreal, Quebec, Canada) prepackaged in brown envelopes. The medication was taken in the presence of nursing staff but not the attending physician. Patients were told to abstain from alcoholic beverages for at least 48 hours. The principal sexual contact, if identified, was treated with a single 2-g dose of metronidazole. Patients were instructed to desist from sexual intercourse until their treatment response had been assessed.

For evaluation, a treatment cure was defined as a patient with a negative wet-mount examination and culture on the first return visit at least one week after

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treatment. The laboratory worker responsible for culturing the organism was not aware of the treatment given. After a treatment cure had been established, most patients were followed at subsequent clinic visits for longer than two weeks after treatment.

STATISTICAL ANALYSIS

χ^2 and Student's *t* tests were used.

Results

One hundred and sixty-three (88%) patients completed the study; 69 were followed in the sexually transmitted diseases clinic (STD) and 94 in the family planning clinic (FP). The age of the patients ranged from 15 to 50 years, with a mean of 22.7 years (23.1 years in the STD clinic and 21.9 years in the FP clinic patients). Mean body weights were also comparable in the two groups of patients (60.0 kg in the STD clinic and 59.1 kg in the FP clinic patients).

CURE RATES

Seventy-two of 86 (84%) patients were cured following a single 2-g dose of metronidazole compared with only 42 of 77 (55%) following a single 1-g dose (table I). The difference in cure rates was significant ($\chi^2 = 16.46$, $P < 0.001$).

TABLE I *Treatment results in patients with trichomoniasis attending the sexually transmitted disease (STD) or family planning (FP) clinic*

Dosage and group	Treatment outcome	
	Cure	Failure
1-g (n = 77)		
STD	21	12
FP	21	23
Total	42	35
2-g (n = 86)		
STD	31	5
FP	41	9
Total	72	14

The results of treatment for patients attending either the STD or FP clinic after each dose regimen are also shown in table I. After the 1-g dose, 21 of 33 (64%) of the STD patients were cured compared with only 21 of 44 (48%) of the patients attending the FP clinic. After the 2-g dose, 31 of 36 (86%) and 41 of 50 (82%) of the STD and FP clinic patients respectively were cured. Neither of these differences was significant ($\chi^2 = 1.93$, $P > 0.1$ and $\chi^2 = 0.31$, $P > 0.5$ respectively).

TIME OF CURE

The time of documentation of a treatment cure (first negative culture result) for the patients in both dosage groups is shown in table II. Approximately 60% of all

TABLE II *Time of documented cure and duration of follow up in patients after single 1-g and 2-g doses of metronidazole*

Dosage group	No of patients cured (and followed up) at:		
	1 week	1-2 weeks	> 2 weeks
1g	25(7)	8(10)	9(25)
2g	39(4)	16(16)	17(52)

patients who were cured had this diagnosis established on their return clinic visit one week after treatment. Of the remaining 40% of treatment cures, approximately half of the patients returned to the clinic either between one and two weeks or more than two weeks after treatment for reculture and confirmation of cure.

DURATION OF FOLLOW UP

Most patients were followed in subsequent clinic visits after their initial negative culture result. In both dosage groups, this follow-up period was longer than two weeks (table II).

SIDE EFFECTS

No severe side effects occurred in either group. Of the 77 patients receiving a 1-g dose, one complained of nausea and vomiting and four of nausea alone. Similarly, of the 86 patients receiving the 2-g dose, one complained of nausea and vomiting and six of nausea alone (one of whom admitted to concurrent alcohol ingestion). An eighth patient complained of an unpleasant taste in the mouth which was severe enough for her to refuse a second course of treatment.

RELATION TO BODY WEIGHT

When treatment outcome was related to body weight it was found to be a significant variable only for those treated with the 1-g dose. For this group, the mean weight of treatment cures was 57 kg ($SD \pm 9.1$ kg) and of failures 63.7 kg ($SD \pm 13.3$ kg) ($t = 2.54$, degrees of freedom = 75, $P < 0.02$). The lighter patients had a much better response although their cure rate of 69% was still less than that overall with the single 2-g dose (table III).

For the 2-g dosage group, the mean weights of treatment cures and failures were 58.9 kg ($SD \pm 11.1$ kg) and 60.7 kg ($SD \pm 11.3$ kg) respectively, which were not significantly different ($t = 0.55$, degrees of freedom = 84, $P > 0.05$).

TABLE III *Treatment results in two patient groups after a single 1-g dose of metronidazole*

Body weight (kg)	Treatment outcome		
	Cure	Failure	Total
≤ 57	24	11	35
> 57	18	24	42

RETREATMENT

Treatment failures after either the 1-g or 2-g dose were retreated with a single 2-g dose of metronidazole. Of 21 patients who had failed initially with 1g, 18 (86%) were cured compared with seven of 10 who had initially failed to respond to the 2-g dose.

Discussion

In a randomised prospective clinical study a single 2-g dose of metronidazole was shown to be significantly more effective than a 1-g dose. The treatment outcome in this study following the 2-g dose was similar to that reported previously in which cure rates ranged from approximately 80% to 95%.^{1-4 7-11} The latter figure occurred in a clinic population where reinfection as a cause of treatment failure was recognised and apparently eliminated.⁸ The proportion of treatment failures that were actually due to reinfection in our study, despite treatment of the principal male consorts and explicit instructions to the patients to avoid sexual intercourse, is unknown.

In the 1-g dosage group, the cure rate of only 55% is in clear contrast to the previously reported 100% cure rate.^{6,7} The reason for this difference is not known but could be partly attributed to reinfection. As a result of randomisation, however, reinfection as a cause of treatment failure would be similar in both dosage groups and therefore should be no greater than 16% (the total failure rate after the 2-g dose). The conclusion from our study is that the single 1-g dose of metronidazole is significantly inferior to the 2-g dose and is not indicated for the routine treatment of symptomatic or clinically evident trichomoniasis.

Interestingly, the body weight of the patient was a significant variable affecting treatment outcome in the 1-g dosage group. To our knowledge, response to metronidazole treatment has not been correlated before with the patient's weight. In patients weighing 57 kg or less, 69% responded to the single 1-g dose but it was still inferior to the overall cure rate of 84% after a 2-g dose. Therefore, even in patients weighing less than 57 kg, a single 1-g dose could not be recommended routinely.

Optimal treatment after failure with a single 2-g dose is not well established. In our study, 70% of patients responded to a second 2-g dose which suggests that this is a reasonable therapeutic approach. Treatment failures after a second 2-g dose when reinfection is not a consideration should be investigated, however, for the possibility of a metronidazole-resistant strain of *Trichomonas vaginalis*,¹²⁻¹⁴ malabsorption of the

drug,¹⁵ or excessive inactivation of metronidazole in the vaginal secretions by other organisms.^{16,17}

It should be emphasised that all patients treated in this study were symptomatic or had clinically evident infection. Asymptomatic trichomoniasis diagnosed on routine vaginal cultures could possibly have a more favourable response to a single 1-g dose of metronidazole, although our study found no relationship between the severity of symptoms and response to treatment.

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